Comparison of Patient versus Physician Reporting of Comorbidities, Results from a Population-Based Cohort of Prostate Cancer Patients

By

Fan Ye

A Master's Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements for
the degree of Master of Public Health in
the Public Health Leadership Program

Chapel Hill

2014

Advisor

Anthony J. Viera, MD, MPH

7/1/14

Date

Second Reader

Ronald C. Chen, MD, MPH

7/8/14

Date

Table of Contents

ABSTRACT

Prostate cancer is the most common malignancy and the second leading cause of cancer mortality in men in the United States, with 240,000 cases diagnosed and 30,000 deaths annually. It is a significant burden for the United States population and health care system due to the disease prevalence, mortality, effects on health related quality of life, as well as cost of treatment. Many different treatment options are available for localized, non-metastatic prostate cancer, such as active surveillance, radical prostatectomy, and radiation therapy, with newer and costlier treatment options being developed. Comparative effectiveness research between these forms of treatment is imperative to determine differences in survival outcomes, health related quality of life, and costs. Here, we reviewed the literature for the frequency of repeat biopsy in prostate cancer patients receiving active surveillance and effects on rate of disease progression, and found insufficient evidence regarding this. Additionally, due to the importance of baseline comorbid conditions in men with prostate cancer in terms of treatment decision making, health related quality of life, and survival outcomes, we conducted a prospective study of 881 men in North Carolina with localized prostate cancer to compare patient versus physician reporting of comorbidities. We calculated percent agreement and its kappa statistic between patient and physician-report for 20 commonly used comorbidities in cancer research. We found that overall, agreement between patient and physician reporting of common comorbidities in newly-diagnosed prostate cancer patients is moderate. In research studies, whether physician reporting, patient reporting, or both should be used to inform treatment decision making and predict survival outcomes is unclear.

Localized Prostate Cancer Patients on Active Surveillance: How Frequently Should We Biopsy Them? A Systematic Review

ABSTRACT

Background: Active surveillance is a strategy in treating low-risk localized prostate cancer patients which defers treatment and monitors patients for disease progression. It is unclear what the optimal surveillance schedule should be. This review assesses the literature for frequency of surveillance biopsy and how that affects detection of disease progression.

Methods: One author performed a systematic review of the literature on active surveillance strategies which used different frequencies of surveillance biopsy using PubMED. The articles were quality rated for internal validity, and external validity.

Results: Twelve (12) studies met the inclusion criteria. Only one study directly assessed the risk of disease progression in relation to the timing of the repeat biopsy, (hazard ratio = 0.40, 95% CI = 0.56-1.58) when the repeat biopsy was performed within 6 months. The remaining studies assessed a mix of probability of disease progression, probability of meeting active surveillance criteria at given time points, percentage of patients who progressed, rate of intervention in patients, and percentage of patients receiving a repeat biopsy without directly analyzing timing of repeat biopsies during active surveillance.

Conclusions: There is insufficient evidence regarding frequency of surveillance biopsy in prostate cancer patients on active surveillance. Future studies directly comparing disease progression or survival rates with frequency of biopsy are needed to fully assess the optimal schedule for surveillance biopsies.

INTRODUCTION

Prostate cancer is the most common cancer and the second leading cause of cancer mortality in men.[1,2] However, unlike other cancers, such as lung or colorectal, there is a wide gap between the incidence and mortality rates of prostate cancer, as more than 240,000 cases are diagnosed yearly compared to roughly 30,000 deaths annually.[1-3] The widespread advent of prostate-specific antigen (PSA) testing for the detection of prostate cancer resulted in a significantly higher incidence without similar increases or decreases in mortality.[4,5] This has raised concerns regarding overdiagnosis, since many of these cancers are localized, small volume, and low grade, and would not have otherwise resulted in any clinical symptoms.[4,5] Overdiagnosis rates of prostate cancer have been estimated to be between 27% and 56%.[4,6] Unfortunately, the natural history of prostate cancer is heterogeneous and not well understood.[3] While some patients may benefit from radical treatment, others may not; as they may suffer from side effects of treatment for a potentially indolent cancer.[7]

More than 90% of newly-diagnosed prostate cancer patients have localized and potentially curable disease.[1] There are many different types of treatment options available for patients with localized prostate cancer, including radical prostatectomy, radiation therapy, and active surveillance.[5] While radical prostatectomy, external beam radiotherapy, and brachytherapy are considered curative therapies for low-risk prostate cancer, they may result in long-term urinary, bowel, and sexual dysfunction, harming patient quality of life.[5,8] An alternative strategy to these curative methods is active surveillance, which defers treatment and actively monitors low risk patients for disease progression, at which point curative treatment is offered.[5,9]

Progression is monitored with a variety of tools, including digital rectal examination (DRE), PSA, rebiopsy, and transrectal ultrasound (TRUS).[7] The rationale behind this is most

men with prostate cancer will not benefit from invasive treatment, and this allows individualization of therapy based on the risk of clinically significant cancer.[10] With this strategy, overtreatment of prostate cancer may be reduced, saving patients from the side effects of treatment as well as saving health resources spent on curative therapy.[10]

Active surveillance strategies vary in terms of which follow-up criteria (DRE, PSA, rebiopsy, and/or TRUS) to use, and how often those tools are used.[7] Prostate biopsies have associated harms, including pain and discomfort, rectal bleeding, change in urine flow, and infection, which may lead to urosepsis and death.[11] Out of the various aforementioned follow-up criteria, prostate biopsy provides the most objective measure of cancer progression.[12] Therefore, therefore the frequency of prostate biopsies should balance the benefit of potential detection of cancer progression with the harms of potential side effects. At the time of this review, it is unclear what the optimal surveillance schedule should be. The aim of this review is to examine men with localized prostate cancer undergoing active surveillance, and if there are any differences in the rate of detection of disease progression requiring intervention, when rebiopsy is performed at intervals less than one year after diagnosis compared to every one year or more after diagnosis.

METHODS

Key questions

Key question 1: Which studies of men with localized prostate cancer undergoing active surveillance assess risk of progression requiring active treatment?

Key question 2: What is the optimal frequency of performing rebiopsy in patients with localized prostate cancer undergoing active surveillance?

Eligibility criteria

For this review, I limited the population of interest to men with localized (node negative, non-metastatic) prostate cancer who are undergoing or have undergone an active surveillance protocol. I chose to exclude men who have previously been treated for prostate cancer because the management and treatment of recurrent prostate cancer is different from that of the initial cancer. The intervention and comparator of interest focus on the frequency of prostate biopsy after diagnosis has already been established and after the patient and provider choose to undergo active surveillance. For this review, I chose to compare a one-year or more interval with less than 1 year. The outcome of interest is detection of disease progression requiring active treatment in the form of surgery or radiation. Although the optimal outcome of interest is benefit in survival or quality of life, these data are unlikely to be available as the natural history of prostate cancer can be very long. Active treatment is instead a surrogate marker as treatment may result in quality of life effects in terms of urinary, bowel, and sexual dysfunction.[8] I chose to examine articles published in the past 10 years (after January 1st, 2004), as prostate cancer detection and treatment methods have evolved greatly. Studies must be performed in Western countries, as these populations are more generalizable to the United States. For inclusion the studies must be longitudinal studies. These predetermined inclusion and exclusion criteria are included in the PICOTTSS table shown in Table 1.

Data sources and searches

To identify articles relevant to the focused question, I searched the MEDLINE database for studies on men with localized prostate cancer undergoing an active surveillance protocol from January 2004 to April 2014. Figure 1 below shows the search and selection process. I

limited my search to studies in English only. I looked for longitudinal studies that studied men with localized prostate cancer who have been on active surveillance, with data on progression of disease detected requiring treatment. For the MEDLINE search I used the focused MeSH terms "Prostatic Neoplasm" or "Prostate Specific Antigen" or the non-MeSH term "Prostate Cancer" combined with the non-MeSH terms "Active Surveillance" and "Longitudinal Studies." The search strategy in MEDLINE is as follows: ((((((prostatic neoplasm[MeSH Major Topic]) OR prostate specific antigen[MeSH Major Topic] OR prostate cancer) AND "active surveillance"))) AND longitudinal studies). This yielded 141 results. Applying the filters "Humans," and "English," narrowed the results to 132. After limiting the studies to those after 2004, this further narrowed the results to 131. Additionally, I augmented my search by hand-searching the reference lists of relevant studies as well as review articles to find any other studies that met the inclusion criteria.

Study selection

I selected and reviewed titles and abstracts of articles retrieved for my focused question in a systematic manner. I used predetermined inclusion and exclusion criteria listed in Table 1. I pulled full text articles for review if the title and abstract seemed relevant for the focused question. These were then reviewed to see if eligibility criteria were still met. I identified one review article in my hand search which listed 7 other studies relevant to the key question. Out of these, 4 were duplicate articles, and the other 3 were included for full text analysis. Studies that had updated versions found in the search were excluded as well. To be included, the studies had to be longitudinal studies of men with localized prostate cancer undergoing active surveillance, from which data on frequency of biopsy and possible disease progression could be extracted.

These studies must have been published in English. The study selection was performed by a single reviewer, however, it would have used two reviewers if additional time and resources were made available.

Data extraction process

I developed a data extraction sheet to gather relevant data. These include sample size, participant characteristics (such as mean/median age, mean/median baseline PSA levels, mean/median Gleason scores, etc.), criteria for active surveillance, criteria for progression, frequency of biopsy after active surveillance enrollment, study results (including median follow-up time, percentage of patients who progressed, percentage of patients that underwent active treatment, and survival outcomes if present), and overall conclusions about the study.

Quality assessment and risk of bias in individual studies

I reviewed the full-text articles meeting all eligibility criteria and independently rated their quality with a single reviewer method. Double review would have been used if adequate time and resources were available. I rated the internal validity of the articles by assessing each for selection bias, measurement bias, and confounding. I assigned grades of "low," "moderate," and "high" for potential sources of bias. I also graded each study for the external validity. The studies were rated overall as "good," "fair," or "poor." In order to qualify for a rating of "good," a study must be well-designed with no more than low risk for selection bias, measurement bias, and confounding. A "fair" rating was given if potential for selection bias, measurement bias, and confounding was mostly moderate. Studies were rated as "poor" if there was excessive risk of bias.

Synthesis of results and data analysis

I combined all relevant abstracted data from the included studies qualitatively and quantitatively in a narrative and table format. Given that study designs, participants, active surveillance initiation criteria, frequency of rebiopsy, and reported outcomes were markedly varied, I chose to focus on describing the studies, results, applicability, and limitations in a qualitative synthesis analysis rather than use a meta-analysis.

Role of funding Source(s)

There was no specified funding for this particular review and there are no known conflicts of interest related to this review.

RESULTS

Search results

The initial PubMed search returned 131 articles for review. A review article found during the search process listed another 7 articles, 4 of which were duplicated from the PubMed search. 22 full-text articles were assessed for eligibility, and out of these, 10 papers were excluded because they were previous non-updated versions of studies that were already included. As such, 12 total articles meeting the inclusion criteria were used in this systematic review (Figure 1).

Study characteristics

All studies used in this review are longitudinal studies (Table 2). The main purpose of the studies varied, although 8 of the 12 studies aimed to describe the results of active surveillance in various patient populations. Other papers studied the role of immediate confirmatory biopsies or

repeated biopsies. 6 studies used 1 year or less as the initial rebiopsy frequency while the other 6 used 1 year or more. The majority of studies all used similar criteria for inclusion of patients in active surveillance, with a combination of PSA, Gleason score, number of positive cores on biopsy, percentage of involvement in each core, clinical stage, and/or PSA velocity. Similarly, progression criteria were similar, although some studies incorporated PSA and clinical stage to measure progression while others used only characteristics derived from prostate biopsy. Baseline patient characteristics for all studies were also relatively similar, with mean or median ages between 62 and 71, and mean or median PSA below 7.5 ng/mL. However, outcome measures were inconsistently reported across studies, as some report median time to biopsy while others do not, and some describe risk of progression while others do not.

Study quality

Internal validity was measured by the presence or absence of selection bias, measurement bias, and confounding. The main risk for selection bias in these studies is that many of the studies were single institution studies, which may lead to some self-selection bias as patients may have chosen to receive treatment at those institutions. Additionally, recruitment of patients was unclear in many studies, although one study specifically mentioned recruiting all eligible patients consecutively.[13] Some studies had a higher rate of drop out than other studies, and it is unclear whether this would have led to differential or non-differential biases. Most of the studies had low to moderate risk of measurement bias, and some studies report an in-house pathologist that reviewed outside biopsy data. The presence of confounding varied greatly between studies. One main source of confounding included progression due to non-biopsy features (including PSA level or velocity, and clinical stage), which limits the interpretation of data. In one study,

risk of confounding was high as the study was performed in community outpatient clinics, so patients could change urologists and the second opinions of those urologists may cause bias towards active treatment.

External validity was evaluated based on whether results from these studies could apply to the wider population of men undergoing active surveillance. Many of these studies were recruited from a single institution, which led to a rating of "fair" for those studies. One study had poor external validity as their criteria for including patients in the active surveillance protocol was stricter than others, leading to inclusion of more patients with favorable risk prostate cancer.[14] One study received a rating of "good" for external validity because patients were recruited from 100 medical centers in 17 countries.[15] Overall, two studies received an overall rating of "good," two studies received an overall rating of "poor," while the other 8 studies were rating as "fair" (Table 3).

Results of studies

Only one study directly assessed risk of progression in relation to timing of repeat biopsy, which found that the hazard ratio for progression was 0.40 (95% CI = 0.56-1.58) when the repeat biopsy was performed within 6 months. The rest of the studies assessed a mix of probability of disease progression, probability of meeting active surveillance criteria at given time points, percentage of patients who progressed, rate of intervention in patients, and percentage of patients receiving a repeat biopsy. Percentage of patients who underwent repeat biopsy varied from 49% to 100% in studies that collected this data. In studies in which repeat biopsy was scheduled to be performed between 0 and 1 year, progression-free survival at 5 years was found to be 76%, 72%, and 67% in 3 studies. One other study had a treatment-free survival at 5 years of 85%. In those

studies where repeat biopsy was scheduled to be performed 1 year or later, progression-free survival was found to be 64% and 59% at 5 years in two different studies, and 67.7% at 4 years.

DISCUSSION

Overall, there is insufficient evidence regarding frequency of surveillance biopsy in prostate cancer patients on active surveillance. In this systematic review, only one article directly assessed the risk of disease progression in relation to the timing of the repeat biopsy, which found that the hazard ratio for progression was 0.40 (95% CI = 0.56-1.58) when the repeat biopsy was performed within 6 months.

There are some major limitations with this review. Firstly, many studies did not report a median or mean time to biopsy. While there were general guidelines for all studies on when to perform a repeat biopsy, patients could receive one earlier in all but 2 studies if they progressed due to non-biopsy factors such as rising PSA levels, increasing PSA velocity, or increasing clinical stage. This makes it difficult to compare data regarding progression-free survival or rates of progression across the intervention and comparison group of performing biopsy before 1 year and 1 year or more after start of active surveillance. Secondly, in this review, we were unable to use the ideal outcome of survival, and instead used the surrogate end point of disease progression. This is not ideal, because this is an intermediate health measure; progression does not necessarily mean that a patient will die from prostate cancer, and conversely, not all patients who exhibit disease progression will die of prostate cancer.[5] Thirdly, only one study out of 12 assessed the harms of prostate biopsy in terms of pain scores, which is an important consideration as the balance of benefits to harms of prostate cancer biopsy frequency should be assessed. In addition, follow-up time for the studies are insufficient. According to Schroder *et al*,

an interval of 10 years is too short to evaluate prostate cancer mortality,[16] but the longest follow up time across all studies in this review is 76 months.

Prostate cancer is a disease which affects and kills many men in the United States. At the same time, there is a concern that prostate cancer is overdiagnosed in patients, leading to unnecessary morbidity and mortality from treatment.[4] Active surveillance is a strategy used to reduce potential overtreatment of patients, and this review of the literature from 2004-2014 examines if there are differences in disease progression requiring active treatment in patients that receive surveillance biopsy at a frequency of less than 1 year following start of active surveillance with patients that receive surveillance biopsy at a frequency of 1 year or more. This review demonstrates that insufficient data are present to fully assess this. Future studies that directly compare disease progression or survival rates with frequency of biopsy are needed to fully assess the optimal schedule for surveillance biopsies.

REFERENCES

1. Siegel R, DeSantis C, Virgo K, et al. Cancer Treatment and Survivorship Statistics, 2012. Vol 62: CA: A Cancer Journal for Clinicians; 2012:220-241.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62(1):10-29.
3. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer.* 2008;112(8):1650-1659.
4. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 2002;94(13):981-990.
5. Bangma CH, Roemeling S, Schröder FH. Overdiagnosis and overtreatment of early detected prostate cancer. *World J Urol.* 2007;25(1):3-9.
6. Johansson JE, Andrén O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA.* 2004;291(22):2713-2719.
7. Bastian PJ, Carter BH, Bjartell A, et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *Eur Urol.* 2009;55(6):1321-1330.
8. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358(12):1250-1261.
9. Aragon-Ching JB. Active surveillance for prostate cancer: has the time finally come? *J Clin Oncol.* 2010;28(16):e265-266; author reply e267.
10. Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol.* 2004;5(2):101-106.

11. Clements R, Aideyan OU, Griffiths GJ, Peeling WB. Side effects and patient acceptability of transrectal biopsy of the prostate. *Clin Radiol.* 1993;47(2):125-126.

12. Al Otaibi M, Ross P, Fahmy N, et al. Role of repeated biopsy of the prostate in predicting disease progression in patients with prostate cancer on active surveillance. *Cancer.* 2008;113(2):286-292.

13. King AC, Livermore A, Laurila TA, Huang W, Jarrard DF. Impact of immediate TRUS rebiopsy in a patient cohort considering active surveillance for favorable risk prostate cancer. *Urol Oncol.* 2013;31(6):739-743.

14. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol.* 2011;29(16):2185-2190.

15. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol.* 2013;63(4):597-603.

16. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med.* 2012;366(11):981-990.

17. Adamy A, Yee DS, Matsushita K, et al. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. *J Urol.* 2011;185(2):477-482.

18. Iremashvili V, Manoharan M, Rosenberg DL, Soloway MS. Biopsy features associated with prostate cancer progression in active surveillance patients: comparison of three statistical models. *BJU Int.* 2013;111(4):574-579.

19. Klotz L. Active surveillance: the Canadian experience with an "inclusive approach". *J Natl Cancer Inst Monogr.* 2012;2012(45):234-241.

20. Kravchick S, Peled R, Cytron S. Watchful waiting and active surveillance approach in patients with low risk localized prostatic cancer: an experience of out-patients clinic with 12-year follow-up. *Pathol Oncol Res.* 2011;17(4):893-897.

21. Patel MI, DeConcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. *J Urol.* 2004;171(4):1520-1524.

22. Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. *J Clin Oncol.* 2011;29(20):2795-2800.

23. Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. *BJU Int.* 2008;101(2):165-169.

24. Thomsen FB, Røder MA, Hvarness H, Iversen P, Brasso K. Active surveillance can reduce overtreatment in patients with low-risk prostate cancer. *Dan Med J.* 2013;60(2):A4575.

Table 1: PICOTTSS Table

	Inclusion	Exclusion
Populations	Men with localized prostate cancer who are undergoing an active surveillance protocol	Men who have previously been treated for prostate cancer
Intervention	Rebiopsy frequency 1 year or more	
Comparison group	Rebiopsy frequency less than 1 year	
Outcomes	Progression of disease so that patient requires active treatment (including surgery or radiation)	
Time for Intervention to Work	Follow-up of at least 12 months after beginning of active surveillance	
Time period for relevant studies/literature	Studies published since 2004	Anything prior to 2004
Setting	Studies conducted in Western countries	All other countries
Study Designs	Longitudinal studies	All other designs

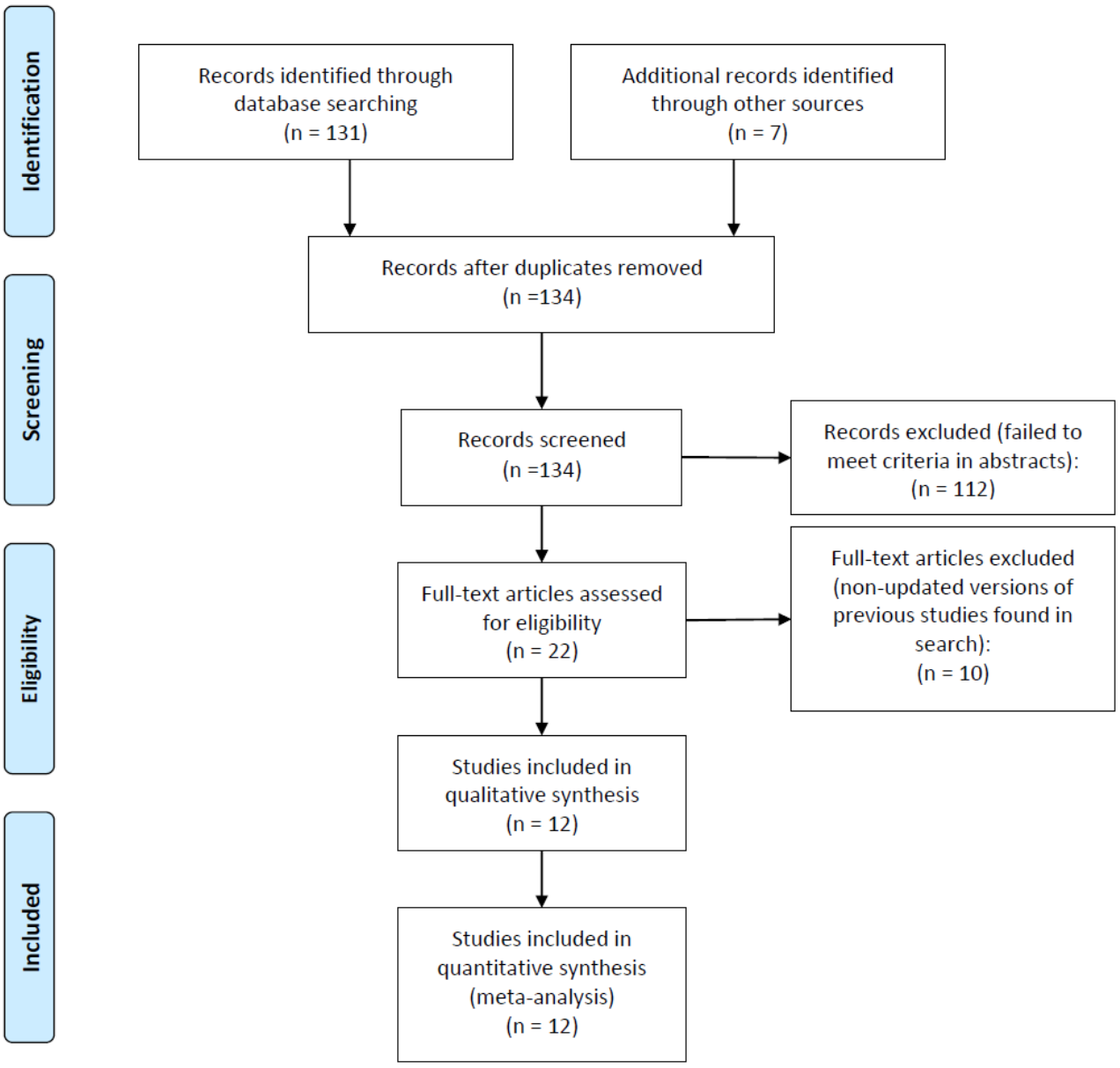

Figure 1: Flow Diagram of Search and Selection of Articles for Review

Table 2: Studies of patients on active surveillance comparing different frequencies of surveillance biopsy

Author, Year (Reference)	Sample Size	Participant Characteristics	Active Surveillance Criteria	Progression Criteria	Frequency of Rebiopsy	Study Results
Adamy 2011[17]	238	• Median age: 64 years • Median time to biopsy: 4.7 mos • Median PSA: 4.1 ng/mL • Patients recruited between 1993-2009	• PSA < 10 ng/mL • Gleason < 7 • ≤ 3 positive biopsy cores • Clinical stage ≤ T2a • Tumor in less than 50% of 1 biopsy core	• PSA ≥ 10 ng/mL (although not included in modified criteria) • Gleason ≥ 7 • >3 positive cores • Clinical stage > T2a • Tumor in greater than 50% of 1 biopsy core	• Confirmatory rebiopsy within 6 mos • 12-18 mos following AS, then 2-3 years following • When clinical exam changed or PSA increased	• 32/238 found to progress on modified criteria (which does not include PSA levels) • 2 and 5 year probability for meeting modified active surveillance criteria of 91% and 76% respectively • 63% of patients receive confirmatory biopsy within 6 mos, 58% of those without cancer • Progression when biopsy 2 is within 6 months of biopsy 1 (HR = 0.4, 95% CI = 0.56-1.58)

Al Otaibi 2008[12]	186	• Median age: 67 years
		• Patients recruited from 1987 and 2006
			• Not specified	• T ≥ cT2b
				• ≥3 positive cores
				• Tumor in greater than 50% of 1 biopsy core
				• Gleason pattern of 4 or greater
					• 12 months following AS
					• When clinical exam changed or PSA increased (checked every 3-6 months)
						• 49% patients were rebiopsied
						• 36% progressed on rebiopsy
						• First repeat biopsy positive in 52% of patients
						• 31% received definitive treatment
						• Probability of disease progression:
						  • 12 mos: 8.7
						  • 24 mos: 23.4
						  • 60 mos: 35.8
						• Median time to treatment: 44 months
						• Median follow-up: 76 mos

Bul 2012[15]	2494	• Median age: 65.8 years
		• Median time to first biopsy: 1.1 years
		• Median PSA: 5.6 ng/mL
		• Patients from PRIAS study starting from 2006
			• PSA ≤ 10 ng/mL
			• PSA density < 0.2 ng/mL
			• <3 positive biopsy cores
			• Gleason ≤ 6
			• Clinical stage T1/T2
				• > 2 positive cores
				• Gleason > 6
				• PSA doubling by < 3 years
					• 1, 4, 7 years
					• Yearly if PSA doubles between 3-10 years
					• PSA every 3 mos for first 2 years, then every 6 mos
						• Repeat biopsy in 1480 men
						• Out of those rebiopsied, 28% reclassified (does not include PSA doubling)
						• Median time to active therapy 1.2 years
						• 21.1% underwent active therapy
						• 387/2494 (15.5%) received treatment due to biopsy progression
						• Active treatment free survival:
						  • 2 yr: 77.3%
						  • 4 yr: 67.7%

Iremashvili 2013[18]	161	• Median age: 62 years • Media PSA: 4.9 ng/mL • All patients recruited from University of Miami from 1994 to 2001	• Gleason ≤ 6 • ≤ 2 positive cores • ≤ 20% involvement of any core • Clinical stage T1-T2a	• Gleason 4/5 cancer • > 2 positive cores • >20% involvement of any core	• Within 1 year of diagnosis, and then 1-2 years following • PSA/DRE checked every 3-4 months	• 100% of patients underwent at least 2 surveillance biopsies • First surveillance biopsy did not contain cancer in more than 50% of patients • 28.6% of patients progressed • Median follow-up: 3.6 years
King 2013[13]	67	• Mean age: 63.9 years • Mean PSA: 5.9 ng.mL • Patients recruited from University of Wisconsin 2007-2011	• Gleason < 7 • PSA < 10 ng/mL • PSA density < 0.15 • < 3 positive biopsy cores • < 50% involvement of any core	• Gleason ≥ 7 • PSA ≥ 10ng/mL • PSA density ≥ 0.15 • ≥ 3 positive biopsy cores • ≥ 50% involvement of any core	Within 6 months	• Average time to rebiopsy: 2.7 mos • 78% underwent rebiopsy • 56% demonstrated no evidence of CaP on rebiopsy • 17% exceeded AS criteria (offered treatment) • 7.7% received treatment

Klotz 2012[19]	450	• Median age: 70.3
		• 85% of patients had PSA ≤ 10
		• 12% had PSA between 10 and 15
		• Patients recruited starting from 1995
			• Between 1995-1999:
			  • Gleason ≤ 6
			  • PSA ≤ 10 for patients < 70
			  • For patients > 70, PSA ≤ 15, Gleason ≤ 3+4
			• After 2000, limited to favorable risk patients only
				• PSA doubling time <3 years (2 years used for first 4 years of study)
				• Gleason score ≥ 4+3
				• "Unequivocal clinical progression"
				• Nodules
					• 6-12 months after starting AS, 3-4 years after
					• PSA every 3 months for 2 years, then every 6 months if stable
						• 48% progression due to PSA doubling time
						• 26% progression due to Gleason upgrading
						• Intervention in 30% patients
						• Likelihood of remaining on surveillance: 84%, 72%, 62% for 2, 5, and 10 years
						• Median follow-up time 6.8 years
						• 5 and 10 year cause specific survival of 99.7% and 97.2%

Kravchick 2011[20]	48	• Mean age: 68.4 years • Mean PSA: 7.4 ng/mL • Patients recruited from community outpatient clinics of 2 health insurance companies from 1998-2006	• PSA ≤ 10 ng/mL • Gleason ≤ 6 • Clinical stage T1a/T1c • < 3 positive biopsy cores • < 30% involvement of any core	Increases in Gleason score or number of positive cores considered indications for active treatment	• 18 months after starting AS or changes in PSA or DRE measured every 3 months	• 28/48 patients underwent rebiopsy • 41.7% underwent active treatment, but half of them met medical criteria • Mean follow-up: 81.1 mos • Pain scores statistically significantly higher in those who underwent 3 or more biopsies
Patel 2004[21]	88	• Mean age: 65.3 years • Mean PSA: 5.9 ng/mL • Patients recruited from Baylor College of Medicine or Memorial Sloan	• Gleason ≤ 7 • Clinical stage T1/T2	Point system with Gleason score increase, PSA velocity increase, DRE/TRUS indications of lesions, and number of cores, needing 3 points to progress	• 6 months after starting active surveillance • Or changes in DRE/TRUS/ PSA indicating progression	• 25% of patients progress • Actuarial 5 and 10 year progression-free survival: 67% and 55% • 31/88 patients treated • Repeat biopsy median of 8 months after diagnosis, 16% progress

		Kettering Cancer Center between 1984 and 2001				• Median time to progression (in cases that progressed): 45 months • Positive rebiopsy significantly associated with progression (p = 0.004) • Median follow-up: 44 months
Porten 2011[22]	377	• Mean age: 61.9 • Median PSA: 5.74 ng/mL • Patients from University of California at San Francisco Urologic Oncology Database included between 1998 and 2009	• PSA < 10 ng/mL • Gleason ≤ 6 with no Gleason 4 or 5 component • Cancer involvement of <33% of biopsy cores • Clinical stage: T1/T2a • Also included men who wished to undergo AS outside these criteria	Increase in primary or secondary Gleason score	• 12-24 months after AS • Repeat PSA and DRE every 3 months	• Median time between biopsies from 12-16 months • 54% of men had 2 or more repeat biopsies • 34% had increase in Gleason grade • 105/377 experienced Gleason upgrade within 30 months of initial diagnosis • 59% of those underwent definitive treatment (76/377 total) • Treatment-free survival rates at 5 years after diagnosis 40% for those who upgraded and 80% for those with no upgrade • Mean follow-up time: 54 months after first repeat biopsy • Another 37/377 chose to undergo treatment despite no change in Gleason score
Soloway 2008[23]	99	• Median age: 67 • Median PSA: 5.77	• Gleason score ≤ 6 • PSA ≤ 15 ng/mL • Clinical stage ≤ T2	• Increase in PSA velocity of PSA doubling time	• 6-12 months after AS, then yearly	• 65% of patients had initial repeat biopsy

		• Patients followed from 1992-2007	• Tumor in less than 50% of two biopsy cores • Excluded men ≥ 80 years of age • > 12 months follow up	• Gleason ≥ 7 • Tumor volume increase • Stage progression	• Repeat PSA and DRE every 3 months	• 8/99 (8%) underwent treatment • 5-year probability of treatment-free survival 85% • Median follow-up: 38 months

Thomsen 2013[24]	167	• Median age: 65 years
		• Median PSA: 6.5
		• Median time to first biopsy: 12.7 months
		• Patients included from 2002 to 2011
			• PSA ≤ 10 ng/mL
			• Gleason ≤ 6
			• Clinical stage T1-2a
			• ≤ 3 positive biopsy cores
			• Tumor in less than 50% of biopsy cores
				• Possible progression (intermediate risk):
				  • PSA double time 3-5 years
				  • Increase in Gleason score to 3+4
				  • cT2b
				• Recommend treatment (high-risk):
				  • PSA doubling time < 3 years
				  • Increase in Gleason score to ≥4+3, or > 3 positive cores
				  • ≥cT2c
					• Within 15 months following AS
					• Repeat PSA and DRE every 3 months
						• Median follow-up: 3.4 years
						• 86% of subjects received rebiopsy
						• 20% progressed on re-biopsy alone
						  • 82% of these within first 2 years
						• 22% reclassified as intermediate risk
						• 17% reclassified as high-risk

Tosoian 2011[14]	769	• Median age: 66 years • Median PSA: 5.0 ng/mL in treated group, 4.7 ng/mL in not treated group • Mean time to first biopsy: 1.3 years	• Gleason ≤ 6 • ≤ 2 positive biopsy cores • Clinical stage ≤ T1c • Tumor in less than 50% of 1 biopsy core • PSA density < 0.15 ng/mL	• Gleason > 6 • > 2 positive biopsy cores • Tumor in more than 50% of 1 biopsy core	• 12 months following AS • "Semiannual" PSA and DRE exams	• Median follow-up: 2.7 years • Compliance with annual surveillance biopsies was 92% for first biopsy • Median survival free of intervention: 6.5 years • 33.2% of men underwent intervention at median of 2.2 years

		• Time between subsequent biopsies: 1.1 years
		• Patients recruited all from Johns Hopkins since 1995
						• 73.7% of all men who underwent intervention did so due to biopsy related disease reclassification
						• Proportion of men intervention-free:
						  • 2 years: 81%
						  • 5 years: 59%
						  • 10 years: 41%

Table 2: Risk of bias in studies

Author, Year (Reference)	Internal Validity			External Validity	Overall Rating	Overall Conclusions
	Selection Bias	Measurement Bias	Confounding			
Adamy 2011[17]	High Unclear how patients were recruited, relatively few lost to follow up.	Low-Moderate Most of the measures are standardized, unlikely that clinical stage or pathology differs	Low – Moderate Other factors such as clinical stage could result in progression, not just biopsy results. PSA levels excluded.	Fair Unclear how this patient group compares to general population	Fair	• The median time to biopsy in this cohort is 4.7 mos, however the hazard ratio for progression is not significant. • About 13% of patients progressed, however it is unclear when the progression occurred.
Al Otaibi 2008[12]	High Recruitment of patients not described	Low 1 out of 2 pathologists reviewed biopsy data	Moderate Other factors such as clinical stage could result in progression, not just biopsy results.	Fair 10% of patients have baseline PSA > 10 ng/mL	Fair	• Results are difficult to interpret for purposes of this review, as less than half of patients received rebiopsy • Progression criteria includes clinical stage, not just biopsy • No analysis for timing of biopsy relating to risk of progression • Long follow up time

						• Disease progression appears most likely in the first 2 years
Bul 2012[15]	Low • PRIAS study (100 medical centers in 17 countries) • Baseline characteristics similar • Low drop out rate (1.7%)	Low-Moderate Internet-based tool (Unclear if abstractors are blinded, and how many there are)	Low	Good Large study across 17 countries and 100 medical centers	Good	• Well done study, no data directly showing frequency of rebiopsy with disease progression • Median time to biopsy is 1.2 years, 59% of patients receive a repeat biopsy • Active treatment free survival at 2 years is 77.3% and 67.7% • This study started recruited patients more recently than most other studies in this review (starting in 2006)
Iremashvili 2013[18]	Moderate Possible self-selection bias due to recruitment at single institution	Low • Outside biopsy slides reviewed by institutional genitourinary pathologist • Clinical stage by attending urologist	Low Progression was only noted due to biopsy features	Fair All patients recruited at single institution, unclear how this compares to general population	Good	• Used 3 models (diagnostic biopsy, first surveillance biopsy, and combination of the two) to analyze risks of progression • However, time to surveillance biopsy was not included
King 2013[13]	Moderate • Recruitment of patients were consecutive • Single institution • Relatively high dropout rate,	Low • Outside biopsy slides reviewed by institutional genitourinary pathologist	Moderate-High Low number of men with prostate cancer choosing active surveillance, these men may more less inclined to	Fair All patients recruited at single institution, lower number of prostate cancer patients choosing	Fair	• Rebiopsy within 6 months, high rate of rebiopsy • Many patients demonstrated lack of prostate cancer on rebiopsy (56%) • 7.7% of patients treated

	but likely non-differential • 22/67 (22%) dropped out due to lack of desire for second biopsy	• Recording of data unlikely to result in measurement differences • Time to rebiopsy limited to 6 months	undergo treatment	active surveillance		
Klotz 2012[19]	Moderate-High Unclear how patients recruited	Low • Recording of data unlikely to result in measurement differences	Moderate Other factors such as clinical stage or PSA kinetics could result in progression, not just biopsy results.	Fair All patients recruited at single institution, lower number of prostate cancer patients choosing active surveillance	Fair	• Goal of study is to assess feasibility of observation with selective delayed intervention in prostate cancer patients (different goal than this review) • Triggers for progression are PSA kinetics and biopsy data • High follow-up time
Kravchick 2011[20]	Moderate-High Enrollment rate of only 17.8%	High Criteria changed in 2004, prior to this date, protocol for repeat biopsy was not present	High Study was done in community outpatient clinics, patients change urologists and second opinions may cause bias towards active treatment	Fair Only included patients between 60-75 years of age, however patients recruited from community outpatient clinics (likely more representative of overall population)	Poor	• Unclear when patients underwent surveillance biopsy (no median or mean time given, since they could receive one at 18 months or from PSA or clinical progression), makes results difficult to interpret in context of this review • Pain scores higher in patients who underwent 3 or more biopsies • Low sample size

Patel 2004[21]	Moderate-High Unclear how patients recruited	Moderate PSA velocity calculated from 3 recorded values in a 1 year period	Moderate-High Excluded patients with significant comorbidities, a population which frequently undergoes active surveillance	Fair Patients recruited at two well-known cancer institutions, unclear how this compares to general population	Poor	• This study started recruited patients more less recently than most other studies in this review (starting in 1984) • Relatively small sample size • Repeat biopsy median of 8 months after diagnosis, 16% progress
Porten 2011[22]	Low-Moderate • All patients from single institution, possible self-selection bias • Only 3% lost to follow up	Low Biopsies all underwent slide review by in-house pathologist	Low Progression was only noted if Gleason score was upgraded	Fair All patients recruited at single institution, unclear how this compares to general population	Good	• Large sample size • Only progressed if Gleason score was upgraded • Unclear how many patients only had 1 repeat biopsy • Unsure of progression free survival
Soloway 2008[23]	Moderate • Unclear how patients were recruited • Baseline characteristics appear similar for overall and treated groups • 7/99 lost to follow up	Moderate Database designed for entering of relevant clinical and pathologic data	Moderate Other factors such as clinical stage or PSA levels could result in progression, not just biopsy results	Fair All patients recruited at single institution, unclear how this compares to general population	Fair	• Sample size is moderate • Unclear when the median biopsy time is • Progression criteria includes clinical stage and PSA, not just biopsy • No analysis for timing of biopsy relating to risk of progression

Thomsen 2013[24]	Low-Moderate All patients from single institution, possible self-selection bias	Low All biopsies re-evaluated by in house uropathologist	Moderate Other factors such as clinical stage could result in progression, not just biopsy results	Fair 6% of patients with Gleason score of 7	Fair	• Relatively high rate of rebiopsy, mean time until first surveillance biopsy listed • Most of those who progressed on rebiopsy did so within first two years • Unfortunately no data directly comparing biopsy time to progression • Sample size is moderate
Tosoian 2011[14]	Moderate • Patients recruited all from Johns Hopkins • Baseline characteristics between treated and untreated mostly similar, although mean and median year of diagnosis in those not treated was 3 years later • 12% dropped out	Low-Moderate Most of the measures are standardized, unlikely that clinical stage or pathology differs	Low	Poor These patients are very-low risk, with stricter enrollment criteria, and all recruited from Johns Hopkins, which may be different from the general population	Fair	• Comparing this to other studies in this review is difficult, because patients recruited are all very-low risk with stricter enrollment criteria • Pros are that mean time until first surveillance biopsy is listed, as well as compliance • Sample size is large

Comparison of Patient versus Physician Reporting of Comorbidities, Results from a Population-Based Cohort of Prostate Cancer Patients

ABSTRACT

Purpose: Baseline patient comorbidities influence treatment decision making and survival outcomes for prostate cancer. Although studies now commonly collect comorbidity information, some via patient report and others through physician report, the agreement between these two information sources is unknown. This study aims to compare patient vs. physician-reported comorbidity in a recently accrued population-based cohort of patients with localized prostate cancer.

Methods: Patients with non-metastatic prostate cancer diagnosed from 2011-13 were recruited via collaboration with the North Carolina Central Cancer Registry. In a sample of 811 patients, phone survey and medical record abstraction for presence/absence of common comorbidities was conducted. We calculated percent agreement and its kappa statistic between patient and physician-report for each condition. We performed subgroup analysis to examine differences in agreement adjusting for age, race, marital status, education level, income, and risk group. Logistic regression was used to examine covariates associated with agreement.

Results: Overall, agreement in 20 comorbidities was moderate. For some conditions (myocardial infarction, cerebrovascular disease, diabetes, HIV/AIDS, and hypertension), agreement was high (kappa > 0.62), but for all other conditions agreement was low to moderate. In subgroup analysis, non-Caucasians have lower patient- vs. physician-report agreement for chronic obstructive pulmonary disease, liver disease, other cancers, and coronary artery disease; but the opposite was true for congestive heart failure, clotting disorders, and inflammatory bowel disease. The findings based on education level were similarly mixed. On multivariable analysis,

older age was significantly associated with lower overall agreement for myocardial infarction, cerebrovascular disease, kidney disease, coronary artery disease, and arrhythmia.

Conclusion: Agreement between patient and physician reporting of common comorbidities in newly-diagnosed prostate cancer patients is moderate. In research studies, whether physician reporting, patient reporting, or both should be used to inform treatment decision making and predict survival outcomes is unclear.

INTRODUCTION

Prostate cancer treatment decision making and survival outcomes are greatly affected by patient baseline comorbid conditions.[1,2] Because the median age of diagnosis of prostate cancer in the United States is 67 years,[3] many patients have other medical conditions concomitantly, such as diabetes, hypertension, cardiovascular disease, and cerebrovascular disease.[4,5] Radical prostatectomy (RP) is a more likely treatment given to younger patients with fewer comorbidities, while radiation therapy (RT) and conservative management (hormone therapy or no treatment) are more likely given to older patients and those with more comorbidities.[3,6-8] There are additional reports demonstrating that patients with fewer comorbidities are more likely to travel long distances to receive treatment, such as proton therapy, at large volume academic centers.[9]

There are a number of treatment options for patients with localized prostate cancer, and the comparative effectiveness of patient outcomes among these options is one of the highest priority research areas according to the Institute of Medicine.[10] Because a patient's comorbid conditions heavily influence treatment selection and directly impact survival and also health-related quality of life outcomes,[1,2,11] observational comparative effectiveness research studies must account for these conditions. A central methodological issue is whether to collect comorbidity data using medical record abstraction or patient report in order to maximize data quality while minimizing cost of data collection. Medical record collection and abstraction depends on the scrupulousness of the documenting provider, requires an abstractor with sufficient medical training, and is more costly to perform.[12] On the other hand, patient report relies on each individual patient accurately knowing his medical history – which may be dependent in part on the health literacy of the patient.

The purpose of this study is to compare patient- vs. physician-reported comorbidity in a population-based cohort of patients with newly diagnosed prostate cancer. We quantify the level of agreement between these two sources on a list of most common comorbid conditions in these men, and assess factors associated with agreement. Given that low socioeconomic status may be associated with poor health literacy,[13,14] we hypothesized that patients who were non-white and those with lower educational attainment would have lower agreement in patient-report vs. physician-report.

METHODS

Data collection

The North Carolina Prostate Cancer Comparative Effectiveness & Survivorship Study (NC ProCESS) is a prospective, population-based cohort of newly-diagnosed localized prostate cancer patients enrolled throughout North Carolina in collaboration with the Rapid Case Ascertainment (RCA) system of the North Carolina Central Cancer Registry. RCA is a research infrastructure with the state Cancer Registry which proactively identified newly-diagnosed prostate cancer patients from all 100 counties in North Carolina from 2011 to 2013. Names of patients, pathology and diagnostic information, as well as their physician's names and addresses were sent to RCA staff by tumor registrars at local hospitals on a weekly basis. These patients were then approached by NC ProCESS staff for study participation. All patients were enrolled before treatment. Participating patients were followed prospectively to collect data on patient-reported outcomes and from medical records.

Outcome Measures

This study included 881 patients enrolled in NC ProCESS with data collected on the following 20 common comorbid conditions: myocardial infarction, congestive heart failure,

peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes, kidney disease, other cancers, human immunodeficiency virus / acquired immune deficiency syndrome, coronary artery disease, arrhythmia, clotting disorders, hypertension, hyperlipidemia, inflammatory bowel disease, asthma, anemia and other blood disorders, and arthritis. These conditions are included in the most commonly used comorbidity indices used in cancer research, including the Charlson Comorbidity Index,[15-17] Adult Comorbidity Evaluation Index (ACE-27),[18] Index of Co-Existent Diseases (ICED),[16,17] and Kaplan-Feinstein Comorbidity Index.[17,19,20] The conditions were assessed two ways – by patient-report via phone survey (with the question: "have you ever been told by a doctor or other health professional that you have [comorbid condition]?") and by medical record abstraction – at the time of study enrollment, which was always before treatment. Medical records were collected from the patient's primary care physician and prostate-cancer providers, including urologist and radiation oncologist, and abstracted for presence of these comorbid conditions.

Statistical Analysis

We describe the presence of each condition based on patient report, medical record abstraction, both, or neither; kappa statistics were used to quantify the level of agreement between patient-report and medical records. Landis and Koch (1977) thresholds were used to classify agreement levels as poor/slight (<0.20), fair (≥0.20 – <0.40), moderate (≥0.40 – <0.60), substantial (≥0.60 – <0.80), or almost perfect (≥0.80).[21] We performed subgroup analyses to determine if kappa varied by age, race, marital status, education level, income, or cancer aggressiveness (as defined by prostate cancer risk group).[22] We then performed logistic regression to assess covariates associated with overall agreement between patient-report and medical records in each condition. The subgroup and multivariable analyses inform our

understanding of whether certain prostate cancer patient subgroups have higher or lower agreement in terms of presence of comorbid conditions from the two data sources. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline cohort characteristics are shown in Table 1. Median age was 65 years. This cohort is diverse with 28% non-Caucasian participants, 32% with high school education or less, and 37% with household income ≤ $40,000. Overall, 28% of patients had a family history of prostate cancer.

Table 2 shows the frequency of patient and physician reporting of each comorbid condition, the level of agreement, and kappa statistics. Agreement was poor or fair (kappa = 0.14-0.39) for peripheral vascular disease, peptic ulcer disease, kidney disease, other cancers, coronary artery disease, arrhythmia, hyperlipidemia, asthma, anemia and other blood disorders, and arthritis; moderate (kappa = 0.43-0.56) for congestive heart failure, chronic obstructive pulmonary disease, liver disease, clotting disorders, and inflammatory bowel disease; and substantial or almost perfect (kappa = 0.62-1.00) for myocardial infarction, cerebrovascular disease, diabetes, human immunodeficiency virus or acquired immune deficiency syndrome, and hypertension. When there was disagreement, both scenarios – a) medical records indicating condition but not reported by patients, and b) patient indicating presence of condition but not indicated in medical records – were observed. For cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, coronary artery disease, and hypertension, medical records were more likely to report the condition than patients (scenario a); while for myocardial infarction, congestive heart failure, peptic ulcer disease, kidney disease, other cancers, arrhythmia, clotting

disorders, hyperlipidemia, asthma, anemia and other blood disorders, and arthritis, patients were more likely to indicate the condition (scenario b).

Subgroup analysis for kappa based on age, race, marital status, education, income, and prostate cancer risk groups for each comorbid condition is shown in Table 3. Kappa which differed by 0.20 or more among subgroups was highlighted, and this difference was observed in 15 conditions. Specifically, kappa differed by patient race in 7 conditions: Caucasian patients had higher kappa in chronic obstructive pulmonary disease, liver disease, cancers other than prostate, and coronary artery disease; while non-Caucasians had higher kappa in congestive heart failure, clotting disorders, and inflammatory bowel disease. Kappa also differed by education in 4 conditions: patients with a high school education or less had higher kappa in kidney disease, clotting disorders, and anemia and other blood disorders; while those with more than a high school education had a higher kappa in inflammatory bowel disease.

In multivariable logistic regression, older age was associated with lower overall agreement in multiple conditions: older than 70 years compared to less than 60 years was associated with lower overall agreement for myocardial infarction (OR = 0.31, 95% CI = 0.12-0.80), cerebrovascular disease (OR = 0.10, 95% CI = 0.01-0.78), kidney disease (OR = 0.18, 95% CI = 0.06-0.52), coronary artery disease (OR = 0.37, 95% CI = 0.20-0.67), and arrhythmia (OR = 0.44, 95% CI = 0.25-0.79); age between 60 and 69 years compared to less than 60 years was associated with lower overall agreement for cerebrovascular disease (OR = 0.11, 95% CI = 0.01-0.85), kidney disease (OR = 0.33, 95% CI = 0.12-0.91), and coronary artery disease (OR = 0.55, 95% CI = 0.31-0.96). Nonwhite race was associated with lower overall agreement for kidney disease (OR = 0.21, 95% CI = 0.10-0.43). A high school education or less compared to

more education was associated with higher overall agreement for anemia and other blood disorders (OR = 2.57, 95% CI = 1.24-5.33).

Across the 20 comorbid conditions assessed in this study, the number of conditions for which there was disagreement between the patient and the physician for each individual patient is shown in Table 5. Patients and physicians agreed on all conditions in 20% of cases. There were 1 or more disagreed conditions in 80% of cases, 2 or more in 48% of cases, 3 or more in 26% of cases, 4 or more in 13% of cases, and 5 or more in 6% of cases.

DISCUSSION

In this study of 881 prostate cancer patients from a diverse, population-based cohort, we examined the agreement between patient-report vs. physician-documentation (via medical record abstraction) in 20 comorbid medical conditions which are commonly included in comorbidity indices used in cancer research. We found that for some conditions (myocardial infarction, cerebrovascular disease, diabetes, HIV/AIDS, and hypertension), agreement was high, but for all other conditions agreement was low to moderate. In subgroup analysis, our hypothesis that non-Caucasians have lower patient- vs. physician-report agreement was demonstrated to be correct for chronic obstructive pulmonary disease, liver disease, other cancers, and coronary artery disease; but we found the opposite to be true for congestive heart failure, clotting disorders, and inflammatory bowel disease. The findings based on educational attainment were similarly mixed. On multivariable analysis, older age was significantly associated with lower overall agreement for myocardial infarction, cerebrovascular disease, kidney disease, coronary artery disease, and arrhythmia.

Accurate assessment of comorbidities is important because prostate cancer treatment decision making is directly affected by a patient's baseline comorbidity status.[1,2] In a 2006 population-based study from the Eindhoven Cancer Registry, patients with no comorbidities as scored using the Charlson Comorbidity Index underwent prostatectomy much more commonly than those with two or more comorbid conditions.[23] Similar practice patterns are seen in the US, where younger and healthier patients commonly receive prostatectomy, while older and those with more comorbid conditions receive radiation therapy or conservative management.[20] Comparative effectiveness research (CER) for localized prostate cancer treatment options (prostatectomy, radiation, active surveillance) is one of the highest priority research areas,[10] and because of the heavy patient selection into different treatment groups, must accurate account for a patient's comorbid conditions in order to reach valid conclusions. Because a patient's comorbid conditions directly impact survival[2] and health-related quality of life,[11] two of the most important outcomes in comparing localized prostate cancer treatment options,[10] a better understanding of how to assess this information addresses one of the most important methodologic issues in CER and will help optimize quality of data versus cost of data collection.

Our study is novel because to our knowledge, there have been no prior studies conducted directly comparing patient- and physician- report of comorbidities specifically in prostate cancer patients. Both sources of information are used in different prostate cancer studies to account for comorbidities.[2,7,23-32] In our literature search, we found a validation analysis from the Prostate Cancer Outcomes Study showing that agreement between medical record review and patient survey exceed 90% in diabetes, myocardial infarction, inflammatory bowel disease, chronic lung disease, heart failure, stroke, bleeding from stomach ulcers, and liver disease; while agreement was lower for arthritis (68%) and hypertension (78%),[24] which are comparable to our results. Our

study differs from this one in that we also assessed kappa statistics to determine if agreement seen is better than chance agreement alone. We also found another study conducted almost 20 years ago by Katz *et al*. in a sample of 170 hospitalized patients.[12] For conditions studied which overlap with our study, kappa values are similar (within 0.20) for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and peptic ulcer disease, while they differ by more than 0.20 for diabetes, kidney disease, and other cancers.[12] However, the Katz study did not specifically include cancer patients, and did not examine whether kappa differed by patient subgroups.[12] Another study published in 1989 of 338 patients with chronic lymphocytic leukemia found kappa values for rheumatoid arthritis and arthritis otherwise unspecified to be 0.08 and 0.27, respectively.[33] Our overall results are fairly consistent with these three prior studies.

Results from this study provide important information for CER investigators, and calls for further methodologic work to examine how to best account for patient comorbidities in comparative research. Importantly, we found low to moderate agreement in some important comorbid conditions, including congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, coronary artery disease, arrhythmia, and asthma. Further, we found lower agreement in several cardiovascular conditions especially in older patients, the patient subgroup most likely to be affected by these conditions.[20] In this study, we obtained and abstracted medical records from the primary care physician and cancer specialists – because we felt these were the most relevant physicians for a prostate cancer patient, and that the primary care physician would be expected to know and document all of a patient's medical conditions. Doing so, we found that patient-report indicated the presence of 11 conditions more often than medical records; i.e. physicians "missed" these comorbid conditions. It is possible that obtaining

records from additional sources would increase agreement with patient-report, but it is also possible that some patients may report presence of certain medical conditions incorrectly. As NC ProCESS obtains longer-term follow-up in these patients, we will be able to assess whether patient-report, medical records, or both best predict patient survival and health-related quality of life outcomes.

Patient reported outcomes research suggests that there is discordance between patient and providers in assessing symptoms, side effects, and quality of life.[34-38] Patients tend to report symptoms earlier and more frequently than do physicians.[35] In terms of quality of life assessment, subjective domain measures result in less agreement between patients and clinicians than the more objective domain measures.[37] Thematically, this fits in with results from our study, in that there are discrepancies between patient and physician reporting of comorbidities, and that patient reporting of comorbidities demonstrates presence of comorbidity more often than physician report.

Data collection from physician sources comes from electronic medical records or traditional paper records. Gathering data from paper charts may be more difficult and costlier to perform, as records typically need to be scanned or may be hard to read. However, the use of electronic medical records by office-based physicians has risen in the United States in the past decade.[39] The implementation of internet-based personal health records (PHRs) will allow patients to access, add content, and share their medical records.[40,41] While this may be limited by health literacy,[42] future PHR usage may result in more accurate information regarding comorbidities in the future, as patients will be able to more easily inform their providers of comorbidities the provider may have missed and vice versa.

This study contains multiple methodological strengths. The NC ProCESS cohort is large and population-based, and the rich diversity of enrolled patients allowed for subgroup analyses to examine agreement by age, race, educational attainment and other factors. Enrollment of patients from the community setting also provides information that is reflective and generalizable to "real world" prostate cancer patients and medical care. In addition, patient-reported comorbidity information and medical records were both obtained prior to prostate cancer treatment, which avoids potential confounding from conditions developed due to treatment and its complications. On the other hand, our description of a meaningful difference in kappa among subgroups (difference of ≥ 0.2) is arbitrary. In our literature search, we were unable to find any existing data on what constitutes a meaningful difference in kappa values. As such, we defined a significant difference to be greater than 0.20 based on the 1977 Landis and Koch kappa classifications,[21] but provide the actual values in Table 3 to allow the reader to make his/her own conclusions.

In conclusion, in a population-based cohort of patients with newly-diagnosed prostate cancer, agreement between patient and physician reporting of common comorbid conditions ranged from low to high. In 4 conditions, medical records were more likely to indicate presence of the condition than patient-report, while in 11 conditions, the converse was observed. This is the first large-scale study to examine information source in comorbidity reporting, a central issue in comparative effectiveness research, and highlights an important methodologic topic which requires further study.

REFERENCES

1. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. *Lancet.* 2003;361(9362):1045-1053.
2. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol.* 2011;29(10):1335-1341.
3. Siegel R, DeSantis C, Virgo K, et al. Cancer Treatment and Survivorship Statistics, 2012. Vol 62: CA: A Cancer Journal for Clinicians; 2012:220-241.
4. What are the key statistics about prostate cancer? 2013; http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed 4/5/2014, 2014.
5. Hall WH, Jani AB, Ryu JK, Narayan S, Vijayakumar S. The impact of age and comorbidity on survival outcomes and treatment patterns in prostate cancer. *Prostate Cancer Prostatic Dis.* 2005;8(1):22-30.
6. Lu-Yao GL, Albertsen P, Warren J, Yao SL. Effect of age and surgical approach on complications and short-term mortality after radical prostatectomy--a population-based study. *Urology.* 1999;54(2):301-307.
7. Harlan LC, Potosky A, Gilliland FD, et al. Factors associated with initial therapy for clinically localized prostate cancer: prostate cancer outcomes study. *J Natl Cancer Inst.* 2001;93(24):1864-1871.
8. Desch CE, Penberthy L, Newschaffer CJ, et al. Factors that determine the treatment for local and regional prostate cancer. *Med Care.* 1996;34(2):152-162.

9. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst.* 2013;105(1):25-32.

10. IOM. IoM: Initial National Priorities for Comparative Effectiveness Research. Washington, DC: The National Academies Press; 2009.

11. Reeve BB, Chen RC, Moore DT, et al. Impact of Comorbidity on Health-Related Quality of Life after Prostate Cancer Treatment: Combined Analysis of Two Prospective Cohort Studies. *BJU Int.* 2014.

12. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Med Care.* 1996;34(1):73-84.

13. Sinclair S, Hammond D, Goodman S. Sociodemographic differences in the comprehension of nutritional labels on food products. *J Nutr Educ Behav.* 2013;45(6):767-772.

14. Knesebeck O, Mnich E, Daubmann A, et al. Socioeconomic status and beliefs about depression, schizophrenia and eating disorders. *Soc Psychiatry Psychiatr Epidemiol.* 2013;48:775-782.

15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

16. Extermann M. Measuring comorbidity in older cancer patients. *Eur J Cancer.* 2000;36(4):453-471.

17. Singh R, O'Brien TS. Comorbidity assessment in localized prostate cancer: a review of currently available techniques. *Eur Urol.* 2004;46(1):28-41; discussion 41.

18. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA.* 2004;291(20):2441-2447.

19. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis.* 1974;27(7-8):387-404.

20. Chen RC, Royce TJ, Extermann M, Reeve BB. Impact of age and comorbidity on treatment and outcomes in elderly cancer patients. *Semin Radiat Oncol.* 2012;22(4):265-271.

21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-174.

22. NCCN Guidelines Prostate Cancer. NCCN; 2013.

23. Houterman S, Janssen-Heijnen ML, Hendrikx AJ, van den Berg HA, Coebergh JW. Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study. *Crit Rev Oncol Hematol.* 2006;58(1):60-67.

24. Klabunde CN, Reeve BB, Harlan LC, Davis WW, Potosky AL. Do patients consistently report comorbid conditions over time?: results from the prostate cancer outcomes study. *Med Care.* 2005;43(4):391-400.

25. Graff JN, Mori M, Li H, et al. Predictors of overall and cancer-free survival of patients with localized prostate cancer treated with primary androgen suppression therapy: results from the prostate cancer outcomes study. *J Urol.* 2007;177(4):1307-1312.

26. Hoffman RM, Barry MJ, Stanford JL, Hamilton AS, Hunt WC, Collins MM. Health outcomes in older men with localized prostate cancer: results from the Prostate Cancer Outcomes Study. *Am J Med.* 2006;119(5):418-425.

27. Thong MS, van de Poll-Franse L, Hoffman RM, et al. Diabetes mellitus and health-related quality of life in prostate cancer: 5-year results from the Prostate Cancer Outcomes Study. *BJU Int.* 2011;107(8):1223-1231.

28. Yancik R, Havlik RJ, Wesley MN, et al. Cancer and comorbidity in older patients: a descriptive profile. *Ann Epidemiol.* 1996;6(5):399-412.

29. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993-1996. *J Clin Epidemiol.* 1999;52(12):1131-1136.

30. Crawford ED, Grubb R, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. *J Clin Oncol.* 2011;29(4):355-361.

31. Houterman S, Janssen-Heijnen ML, Verheij CD, Kil PJ, van den Berg HA, Coebergh JW. Greater influence of age than co-morbidity on primary treatment and complications of prostate cancer patients: an in-depth population-based study. *Prostate Cancer Prostatic Dis.* 2006;9(2):179-184.

32. Post PN, Hansen BE, Kil PJ, Janssen-Heijnen ML, Coebergh JW. The independent prognostic value of comorbidity among men aged < 75 years with localized prostate cancer: a population-based study. *BJU Int.* 2001;87(9):821-826.

33. Linet MS, Harlow SD, McLaughlin JK, McCaffrey LD. A comparison of interview data and medical records for previous medical conditions and surgery. *J Clin Epidemiol.* 1989;42(12):1207-1213.

34. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol.* 2006;7(11):903-909.

35. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst.* 2009;101(23):1624-1632.

36. Brunelli C, Kaasa S, Knudsen AK, Hjermstad MJ, Pigni A, Caraceni A. Comparisons of patient and physician assessment of pain-related domains in cancer pain classification: results from a large international multicenter study. *J Pain.* 2014;15(1):59-67.

37. Janse AJ, Gemke RJ, Uiterwaal CS, van der Tweel I, Kimpen JL, Sinnema G. Quality of life: patients and doctors don't always agree: a meta-analysis. *J Clin Epidemiol.* 2004;57(7):653-661.

38. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. *J Clin Epidemiol.* 2002;55(11):1130-1143.

39. Hsiao C, Hing E, Socey TC, Cai B. Electronic medical record/electronic health record systems of office-based physicians: United States, 2009 and preliminary 2010 state estimates. National Center for Health Statistics; 2010.

40. Ahmed S, Berzon RA, Revicki DA, et al. The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. *Med Care.* 2012;50(12):1060-1070.

41. Brennan PF, Downs S, Casper G, Kenron D. Project HealthDesign: stimulating the next generation of personal health records. *AMIA Annu Symp Proc.* 2007:70-74.

42. Woods SS, Schwartz E, Tuepker A, et al. Patient experiences with full electronic access to health records and clinical notes through the My HealtheVet Personal Health Record Pilot: qualitative study. *J Med Internet Res.* 2013;15(3):e65.

Table 1: Characteristics of patients in this study

Characteristic	Number of Patients (N=881)	%
Age, years (median: 65, range: 41-80)		
<60	223	26
60-69	419	49
≥70	210	25
Race		
White	633	72
Nonwhite	248	28
Marital Status		
Married	710	81
No/unknown	171	19
Education		
High school graduate or less	281	32
Some college or more	589	67
Unknown	11	1
Income		
≤$40,000	322	37
>$40,000	522	59
Unknown	37	4
NCCN Risk Group		
Low	458	52
Intermediate	327	37
High	94	11

Abbreviations: PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network

Table 2: Comparison of patient vs. physician reporting of comorbid conditions

Comorbid Condition	(AGREE) Patient No, Physician No N(%)	(DISAGREE) Patient No, Physician Yes N(%)	(DISAGREE) Patient Yes, Physician No N(%)	(AGREE) Patient Yes, Physician Yes N(%)	Overall Agreement (%)	Kappa
Myocardial Infarction	771 (89)	10 (1)	40 (5)	47 (5)	94	0.62
Congestive Heart Failure	821 (94)	6 (1)	29 (3)	14 (2)	96	0.43
Peripheral Vascular Disease	821 (94)	17 (2)	21 (2)	10 (1)	95	0.32
Cerebrovascular Disease	804 (93)	18 (2)	9 (1)	38 (4)	97	0.72
COPD	778 (90)	31 (4)	21 (2)	38 (4)	94	0.56
Peptic Ulcer Disease	773 (89)	17 (2)	65 (7)	15 (2)	91	0.23
Liver Disease	841 (97)	10 (1)	9 (1)	10 (1)	98	0.48
Diabetes	649 (75)	28 (3)	5 (1)	188 (22)	97	0.90
Kidney Disease	825 (95)	14 (2)	27 (3)	4 (<1)	95	0.14
Other Cancers	787 (91)	9 (1)	64 (7)	9 (1)	92	0.17
HIV / AIDS	865 (100)	0 (0)	0 (0)	4 (<1)	100	1.00
Coronary Artery Disease	723 (83)	85 (10)	27 (3)	34 (4)	87	0.31
Arrhythmia	716 (82)	17 (2)	98 (11)	39 (4)	86	0.34
Clotting Disorders	834 (96)	4 (<1)	21 (2)	10 (1)	97	0.43
Hypertension	279 (32)	72 (8)	61 (7)	457 (53)	85	0.68
Hyperlipidemia	281 (32)	107 (12)	172 (20)	309 (36)	68	0.36
Inflammatory Bowel Disease	848 (97)	3 (<1)	11 (1)	7 (1)	98	0.49
Asthma	780 (90)	3 (<1)	63 (7)	24 (3)	93	0.39
Anemia/Blood Disorders	806 (93)	8 (1)	48 (6)	7 (1)	94	0.18
Arthritis	519 (60)	14 (2)	288 (33)	48 (6)	66	0.14

Abbreviations: COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome

Table 3: Agreement (kappa) of comorbid conditions based on patient characteristics*

Comorbid Condition	Age			Race		Marital Status		Education		Income		NCCN risk group		
	<60 (N=223)	60-69 (N=419)	≥70 (N=210)	White (N=633)	Nonwhite (N=248)	Married (N=710)	Other (N=171)	≤HS (N=281)	>HS (N=589)	≤$40k (N=322)	>$40k (N=522)	Low (N=458)	Intermediate (N=327)	High (N=94)
Myocardial Infarction	0.65	0.66	0.53	0.61	0.68	0.63	0.59	0.65	0.61	0.62	0.64	**0.69**	**0.46**	**0.79**
Congestive Heart Failure	**0.59**	**0.37**	**0.48**	**0.28**	**0.62**	**0.31**	**0.58**	**0.63**	**0.27**	**0.51**	**0.27**	**0.44**	**0.41**	**1.00**
Peripheral Vascular Disease	**0.21**	**0.20**	**0.50**	0.34	0.26	0.32	0.32	0.23	0.38	**0.14**	**0.42**	0.26	0.38	0.38
Cerebrovascular Disease	**0.94**	**0.69**	**0.67**	0.70	0.75	0.71	0.73	0.70	0.74	0.68	0.79	0.75	0.66	0.78
COPD	0.52	0.54	0.60	**0.61**	**0.40**	0.57	0.52	0.62	0.49	0.57	0.50	**0.57**	**0.61**	**0.39**
PUD	0.25	0.21	0.26	0.20	0.32	0.19	0.37	0.34	0.16	0.33	0.15	0.21	0.24	0.27
Liver Disease	0.53	0.41	0.49	**0.57**	**0.24**	**0.43**	**0.65**	0.49	0.51	**0.71**	**0.44**	0.55	0.49	0.38
Diabetes	0.90	0.90	0.89	0.89	0.91	0.90	0.89	0.89	0.90	0.91	0.88	0.92	0.88	0.84
Kidney Disease	**0.00**	**0.21**	**0.08**	0.09	0.15	0.15	0.12	**0.25**	**-0.01**	0.19	0.08	**0.22**	**0.08**	**-0.02**
Other Cancers	0.09	0.19	0.19	**0.20**	**-0.02**	0.14	0.27	0.16	0.17	0.06	0.21	0.15	0.19	0.32
HIV / AIDS	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Coronary Artery Disease	0.38	0.34	0.22	**0.37**	**0.14**	0.34	0.18	0.23	0.35	0.35	0.29	0.28	0.34	0.38
Arrhythmia	**0.31**	**0.44**	**0.19**	0.36	0.28	0.37	0.26	0.37	0.33	0.23	0.41	0.32	0.37	0.42
Clotting Disorders	**0.60**	**0.24**	**0.41**	**0.36**	**0.60**	0.47	0.31	**0.59**	**0.31**	0.56	0.38	**0.30**	**0.61**	**0.55**
Hypertension	0.75	0.67	0.63	0.69	0.64	0.70	0.58	0.63	0.70	0.62	0.72	0.66	0.69	0.74
Hyperlipidemia	0.45	0.34	0.31	0.32	0.46	0.35	0.41	0.41	0.34	0.36	0.37	**0.30**	**0.40**	**0.52**
Inflammatory Bowel Disease	**0.40**	**0.70**	**-0.01**	**0.45**	**1.00**	0.51	0.39	**-0.01**	**0.60**	0.49	0.49	0.42	0.49	0.66
Asthma	0.48	0.38	0.37	0.35	0.50	0.39	0.39	0.47	0.35	0.46	0.31	**0.26**	**0.48**	**0.71**
Anemia/Blood Disorders	**0.11**	**0.12**	**0.38**	0.21	0.08	0.20	0.11	**0.34**	**0.13**	0.13	0.24	0.16	0.19	0.20
Arthritis	0.20	0.11	0.13	0.11	0.20	0.12	0.20	0.14	0.14	0.12	0.17	0.12	0.13	0.26

*A kappa difference of ≥ 0.2 among subgroups is highlighted

Abbreviations: COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome

Table 4: Multivariable logistic regression for agreement in each comorbid condition*

Characteristic	Myocardial Infarction	CHF	PVD	Cerebro-vascular	COPD	PUD	Liver Disease	Diabetes	Kidney Disease	Other Cancers
Age										
<60	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
60-69	0.48 (0.19, 1.20)	0.35 (0.12, 1.06)	0.62 (0.26, 1.52)	**0.11 (0.01, 0.85)**	0.61 (0.28, 1.31)	0.62 (0.33, 1.14)	0.80 (0.27, 2.37)	0.62 (0.24, 1.63)	**0.33 (0.12, 0.91)**	1.09 (0.57, 2.08)
≥70	**0.31 (0.12, 0.80)**	0.35 (0.10, 1.17)	0.76 (0.27, 2.14)	**0.10 (0.01, 0.78)**	0.69 (0.29, 1.68)	0.75 (0.36, 1.54)	1.52 (0.35, 6.63)	0.78 (0.25, 2.42)	**0.18 (0.06, 0.52)**	0.58 (0.30, 1.14)
Race										
White	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Nonwhite	1.41 (0.65, 3.05)	0.65 (0.28, 1.50)	1.26 (0.56, 2.86)	0.86 (0.34, 2.17)	0.94 (0.48, 1.86)	1.21 (0.67, 2.20)	0.71 (0.24, 2.06)	0.88 (0.37, 2.13)	**0.21 (0.10, 0.43)**	1.94 (0.94, 4.03)
Marital Status										
Other	1.30 (0.63, 2.71)	1.84 (0.79, 4.28)	1.47 (0.67, 3.23)	1.47 (0.58, 3.74)	1.96 (1.02, 3.76)	0.85 (0.44, 1.63)	1.35 (0.41, 4.49)	1.37 (0.55, 3.40)	1.89 (0.88, 4.05)	1.04 (0.53, 2.06)
Married	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Education										
High school graduate or less	1.06 (0.54, 2.11)	1.45 (0.61, 3.43)	0.64 (0.30, 1.33)	0.84 (0.35, 2.03)	0.81 (0.43, 1.54)	1.06 (0.61, 1.84)	0.80 (0.28, 2.33)	0.71 (0.31, 1.63)	0.80 (0.39, 1.65)	1.17 (0.64, 2.13)
Some college or more	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Income										
≤$40,000	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
>$40,000	1.67 (0.84, 3.31)	0.90 (0.42, 2.28)	1.61 (0.75, 3.46)	1.82 (0.72, 4.65)	1.49 (0.77, 2.89)	1.31 (0.75, 2.27)	0.38 (0.10, 1.38)	0.80, 0.33, 1.90)	0.92 (0.43, 1.98)	0.91 (0.50, 1.66)
NCCN Risk Group										
Low	REF	+	REF	REF	REF	REF	REF	REF	REF	REF
Intermediate	0.75 (0.41, 1.38)	+	0.87 (0.43, 1.77)	0.82 (0.35, 1.91)	1.59 (0.82, 3.07)	1.12 (0.68, 1.84)	0.69 (0.25, 1.89)	0.74 (0.33, 1.66)	0.99 (0.49, 2.01)	1.42 (0.83, 2.44)
High	2.79 (0.64, 12.15)	+	1.55 (0.44, 5.46)	1.02 (0.27, 3.78)	0.93 (0.40, 2.15)	1.95 (0.75, 5.10)	0.45 (0.11, 1.80)	0.56 (0.19, 1.64)	1.18 (0.41, 3.43)	2.33 (0.81, 6.71)

Characteristic	CAD	Arrhythmia	Clotting	Hypertension	Hyperlipidemia	IBD	Asthma	Anemia/Blood disorders	Arthritis
Age									
<60	REF	REF	REF	REF	REF	REF	REF	REF	REF
60-69	**0.55 (0.31, 0.96)**	0.77 (0.45, 1.33)	0.67 (0.23, 1.98)	0.77 (0.47, 1.26)	0.78 (0.54, 1.13)	1.04 (0.24, 4.42)	0.56 (0.28, 1.11)	0.76 (0.39, 1.49)	0.74 (0.52, 1.06)
≥70	**0.37 (0.20, 0.67)**	**0.44 (0.25, 0.79)**	0.53 (0.17, 1.72)	0.71 (0.41, 1.23)	0.75 (0.49, 1.15)	0.54 (0.13, 2.31)	0.72 (0.32, 1.63)	1.35 (0.55, 3.28)	0.71 (0.46, 1.07)
Race									
White	REF	REF	REF	REF	REF	+	REF	REF	REF
Nonwhite	0.74 (0.45, 1.22)	0.97 (0.59, 1.60)	1.16 (0.40, 3.38)	1.07 (0.67, 1.71)	0.13 (0.87, 1.81)	+	0.94 (0.48, 1.81)	0.77 (0.40, 1.49)	1.20 (0.84, 1.72)
Marital Status									
Other	REF	REF	REF	REF	REF	REF	REF	REF	REF
Married	2.2 (1.34, 3.62)	1.33 (0.80, 2.22)	3.05 (1.20, 7.71)	1.39 (0.85, 2.25)	0.90 (0.60, 1.34)	1.53 (0.39, 6.04)	1.91 (1.01, 3.64)	1.30 (0.65, 2.60)	0.77 (0.52, 1.14)
Education									
Some college or more	REF	REF	REF	REF	REF	REF	REF	REF	REF
High school graduate or less	0.78 (0.49, 1.24)	0.88 (0.55, 1.39)	0.80 (0.32, 2.02)	0.86 (0.56, 1.34)	1.18 (0.83, 1.67)	0.70 (0.21, 2.37)	1.27 (0.67, 2.39)	**2.57 (1.24, 5.33)**	0.99 (0.71, 1.39)
Income									
≤$40,000	REF	REF	REF	REF	REF	REF	REF	REF	REF
>$40,000	0.63 (0.38, 1.04)	1.13 (0.70, 1.82)	0.37 (0.13, 1.07)	1.06 (0.67, 1.68)	1.26 (0.88, 1.79)	0.56 (0.15, 2.12)	0.82 (0.43, 1.54)	1.57 (0.81, 3.04)	1.32 (0.94, 1.86)
NCCN Risk Group									
Low	REF	REF	REF	REF	REF	REF	REF	REF	REF
Intermediate	1.26 (0.81, 1.96)	1.40 (0.90, 2.17)	2.42 (0.88, 6.67)	1.31 (0.67, 2.56)	1.24 (0.90, 1.69)	1.80 (0.47, 6.85)	1.29 (0.74, 2.26)	1.74 (0.92, 3.29)	1.01 (0.74, 1.37)
High	2.04 (0.92, 4.49)	2.10, 0.96, 4.59)	1.21 (0.34, 4.32)	1.18 (0.78, 1.79)	1.63 (0.96, 2.75)	0.86 (0.18, 4.21)	2.99 (0.89, 10.0)	1.02 (0.43, 2.43)	1.37 (0.83, 2.27)

*Significant association is highlighted

+Excluded from analysis due to insufficient number of samples in these categories

Values are odds ratio (95% confidence interval)

Abbreviations: CHF = congestive heart failure; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; PUD = peptic ulcer disease; CAD = coronary artery disease; IBD = inflammatory bowel disease

Table 5: Number of disagreed conditions across all comorbidities per patient

	Number	Percent
0 disagreed conditions	178	20
1 or more	698	80
2 or more	424	48
3 or more	232	26
4 or more	114	13
5 or more	55	6

Acknowledgements

I would like to sincerely thank Dr. Ronald Chen for his mentoring, patience, support, teaching, dedication, and critical reading of my master's paper. I would also like to thank my advisor, Dr. Anthony Viera, for his teaching, support, and critical reading of my master's paper. My gratitude also goes to Dr. Russell Harris for his aid in writing the systematic review portion of this paper.

I would like to also thank Laura Hendrix and Rebecca Green for their aid, advice, and teaching on the statistical methods used in this paper, as well as Deborah Usinger, Brittney Barbosa, and Kiayni Spearman for their assistance in the timely collection of data.

Finally, I would like to thank all others who contributed to this paper: Mark Waddle, Dr. William Carpenter, Dr. Bryce Reeve, Kevin Pearlstein, Angela Lucero, and Dr. Paul Godley. Without all of you, this master's paper would not be possible. Thank you all very much.